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EXAMINER	
SHAFER, SHULAMITH H	
ART UNIT	**PAPER NUMBER**
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/810,358	CHEN ET AL.	
	Examiner	Art Unit	
	SHULAMITH H. SHAFER	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *20 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-8 and 11-45* is/are pending in the application.

4a) Of the above claim(s) *13-15 and 24-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-8,11,12,16,-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

This Office Action is in response to Amendment and Remarks of 20 March 2009.

The amendment received 20 March 2009 has been entered. Claims 1, 3, 5-8, and 11-45 are pending in the instant application. Claims 5 and 22 have been amended and the amendment made of record. Claims 13-15 and 24-45 stand withdrawn as being drawn to a non-elected invention.

Claims 1, 3, 5-8, 11, 12, and 16-23 are under consideration.

Withdrawn Rejections

The rejection of Claim 5 under 35 U.S.C. 112, second paragraph, is withdrawn in light of Applicants' amendment of the claim to correct claim dependency.

The rejection of Claim(s) 1, 3, 5-8, 11, 12 and 16-21 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement (scope of enablement rejection) is withdrawn, in part, in light of applicants' persuasive arguments and in light of further consideration of the art which teaches measurement of spontaneous and stimulated cytokine production in cultures of PBMC (See, for example, O'Gorman et al. 2008. Handbook of Human Immunology, 2nd edition, pages 154 and 155, CRC Press). Therefore, the part of the rejection as applied to measurement of cytokine levels in a biological sample wherein the biological sample comprises peripheral blood mononuclear cells that have **not** been stimulated is withdrawn.

Maintained Rejections

35 U.S.C. § 112, Second Paragraph:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22 and 23 stand rejected under 35 U.S.C. 112, 2nd paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As previously discussed, Claim 22 is vague and indefinite for reciting a "kit comprising a first measuring element or system for measuring the level of at least one anti-inflammatory cytokine…..and a second measuring element or system for measuring the level of at least one pro-inflammatory cytokine….". The claim, drawn to an element or system does not recite any structural limitations. It is unclear how an element or system could be utilized to measure levels of a protein, such as a cytokine. The claim does not recite what such element or system must comprise (i. e. antibodies to detect cytokines, components of a chromatography or bioassay system, etc). The disclosure [paragraph 0078 of PGPUB 20040228837, the PGPUB of the instant application] recites a number of possible examples of assays and methods for detecting cytokines, but does not present a limiting definition or description of what the kit of the instant invention comprises. Therefore, the metes and bounds of the claim cannot be determined.

Claim 23 is included in this part of the rejection as dependent upon a rejected claim.

Applicants traverse the rejection (Remarks of 20 March 2009, page 11, last paragraph bridging page 13, first paragraph).

The reasons for the traversal are:

Claim 22 does specify two elements: A kit comprising *inter alia a first measuring element or system* for measuring the level of at least one anti-inflammatory cytokine in a biological sample from a mammalian subject before treatment and at least one time point after or during treatment, *a second measuring element or system* for measuring the level of at least one pro-inflammatory cytokine in a biological sample from said mammalian subject before treatment, and at least one time point after or during treatment, and usage instructions. Example structure and measuring elements or

systems are described in the specification, starting at page 12, line 13, wherein it is stated that: "Such measuring elements or systems may include those known to one skilled in art, non-limiting examples of which include immunosorbent assays, enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), multiplexed ELISAs on microarray platforms, multiplexed ELISAs using coded microspheres coupled with a flow cytometer detection systems, bioassays, Western blots, chromatograph-based separation systems, RT-PCR, competitive reverse transcription PCR, Northern blots, gene arrays, direct measurement of m-RNA, and mixtures thereof,...". Claim 22 is now amended to recite the structural element of instructions provided to a user. Both measuring elements or systems measure cytokines. One system measures anti-inflammatory cytokines and the other system measures pro-inflammatory cytokines. The instructions relate the two measuring elements or systems.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

The elements or systems recited in the claim do not comprise any structural limitations or concrete elements as would be commonly understood to be components of a kit, which is understood to be a product (see In re Venezia 530 F.2d 956 CCPA 1975); rather the claim is drawn to unspecified systems or elements for performing steps to be used in the method of the claimed invention *i.e.*, the claim is directed to an unspecified method of measuring pro and anti inflammatory cytokines, and does not recite components which would make up the claimed kit. The disclosure, as noted above, recites a number assays and methods for detecting cytokines that are well-known in the art. It is unclear how applicants can claim these assays and/or methods as novel kits.

With respect to the structural element of printed material or instructions, the fact that the printed material refers to two measuring elements or systems does not distinctly identify what applicants consider the components of the kit of the instant invention. Does the kit comprise containers of antibodies to detect the cytokines, chromatographic material, a microarray, etc?

35 U.S.C. § 112, First Paragraph:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of Claim(s) 1, 3, 5-8, 11, 12 and 16-21 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement (**scope of enablement rejection**) is maintained for reasons of record and for reasons set forth below.

The specification, while being enabling for a method of determining the efficacy of a treatment of inflammatory diseases of the bowel in mammals *in vivo*:

wherein a treatment comprises any treatment for inflammatory diseases of the bowel other than those treatments comprising direct administration of anti-inflammatory cytokines or compositions which directly inhibit pro-inflammatory cytokines

does not reasonably provide enablement for a method of determining the efficacy of a treatment of inflammatory diseases of the bowel in mammals *in vivo*:

wherein a treatment comprises direct administration of anti-inflammatory cytokines or compositions which directly inhibit pro-inflammatory cytokines

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

As previously noted, the art teaches that IB diseases are controlled by a wide variety of treatments including administration of cytokines and anti-cytokines, including anti-TNF-α and IL-10 (Papadikis et al, page 295, 4th paragraph, cited on previous IDS and previous Office Action). Thus, patients may be treated by administration of IL-10 and/or antibodies to pro-inflammatory cytokines. Direct administration of IL-10 and/or antibodies which bind to pro-inflammatory cytokines would result in raising the levels of IL-10 in a biological sample and/or decreasing the levels of pro-inflammatory cytokines.

This increase in IL-10 levels and/or decrease in pro-inflammatory cytokines would naturally result in a shift in the ratio of levels IL-10 to levels of IL-12 or ratio of levels IL-10 to levels of TNF-α, or ratio of levels IL-10 to levels of IFNγ but these changes would not be indicative of efficacy of treatment. These changes would arise as a direct result of administration of IL-10 and/or antibodies which bind to pro-inflammatory cytokines.

Applicants traverse this outstanding rejection (Remarks of 20 March 2009, page 14, 2nd paragraph bridging page 15, 2nd paragraph). The reasons for the traversal are:

Even though such treatments may be known, and the subject's response might be due to the administration of an anti-inflammatory cytokine (which would raise the level of anti-inflammatory cytokine) or antibody to a pro-inflammatory cytokine (which would lower the levels of pro-inflammatory cytokine) the methods of the Application, and studying changes in ratios of cytokines can be used to study the subject's response to the treatment, and to determine the effect of the treatment, without undue experimentation.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

The claims are drawn to methods of evaluating the efficacy of treatment of IBD by determining changes in the ration of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine. One of ordinary skill would anticipate that the administered treatment would result in some physiological change. This physiological change would result in a change in levels of pro-inflammatory or anti-inflammatory cytokines or both. These changes in cytokine levels would be evaluated by determining the change in the ratio of levels of anti-inflammatory to pro-inflammatory cytokines.

However, the art-recognized treatments discussed above (administration of anti-inflammatory cytokines, or antagonists of pro-inflammatory cytokines), by themselves, would result in increasing IL-10 levels and/or decreasing pro-inflammatory cytokine levels in biological samples drawn from the patient. These treatments would result in a

change in the ratios of levels IL-10 to levels of IL-12 or levels of TNF-α or levels of IFN-γ. Such changes would not be a response to treatment, but a result of administration of the therapeutic agents. One of ordinary skill in the art could not determine if these changes (changes in ratio of levels of anti-inflammatory cytokines) would be indicative of efficacy of treatment or are a result solely of administration of therapeutic compounds. There are no teachings in the disclosure to enable the skilled practitioner to differentiate between these possibilities without undue experimentation.

35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of Claim 22 under 35 U.S.C. 102(b) as being anticipated by Vignali (2000 Journal of Immunological Methods 243:243-255) is maintained for reasons of record and for reasons set forth below.

Claim 22, given its broadest reasonable interpretation, is drawn to a kit for measuring cytokines in a biological sample from a mammalian subject. There are no structural limitations recited as to the contents of said kit. A kit claim is directed to a product, and not to a method, so the intended use of the kit, and a recitation of when such measurements are to be performed is not given patentable weight. The claim does not explicitly recite any specific structural elements or components; thus art which teaches components used for measurement of the recited cytokines will anticipate the limitations of the claim.

As previously stated, Vignali teaches a FlowMetrix System of quantifying the concentration of 15 cytokines simultaneously in a 100 µl sample (page 248, 2nd column, section 60). The technology utilizes microspheres as the solid support for an immunoassay which are subsequently analyzed on a flow cytometer (abstract). Among

the cytokines which may be measured in culture supernatants of stimulated peripheral blood mononuclear cells (T cells) are IL-4, IFN-γ and IL-12, which are among the cytokines recited in claim 22 of the instant invention. Once the concentration of cytokines are determined, the ratios may easily be determined by dividing the concentrations of anti-inflammatory cytokines by the concentrations of pro-inflammatory cytokines. The skilled artisan may then draw conclusions by comparing ratios.

Applicants traverse this rejection (Remarks of 20 March 2009, page 16, 4th paragraph bridging page 15, 2nd paragraph). The reasons for the traversal are:

Vignali does not disclose a kit for measuring the particular cytokines recited in Claim 22, in a supernatant from cells cultured from a biological sample. Vignali simply discusses assay methods that can be used to measure various analytes and discusses the advantages and disadvantages of various assay methods and devices.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

Vignali teaches use of a FlowMetrix System, a kit for measuring cytokines. As there are no structural limitations recited in the claims as to the contents of said kit, a reasonable interpretation of the claims could interpret a kit to comprise, for example, antibodies to cytokines in a vial or test tube. The FlowMetrix system can be used at any time point of a treatment protocol to measure pro- and anti-inflammatory cytokines. Vignali teaches use of the FowMetrix assay kit to quantify cytokines in a variety of systems, including cytokine production by stimulated $CD4^+$ T cells in culture (culture supernatants) (page 248, 2nd column, 4th paragraph). The FlowMetrix system comprises microspheres as the solid support for an immunoassay which are subsequently analyzed on a flow cytometer. Applicants disclosure [paragraph 0078] teaches that measuring elements or systems may include immunoassays or multiplexed ELISAs using coded microspheres coupled with a flow cytometer detection systems. These methods encompass the FlowMetrix system taught by Vignali.

35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of Claim 23 under 35 U.S.C. 103(a) as being unpatentable over Vignali (2000 Journal of Immunological Methods 243:243-255) as applied to claim 22 is maintained for reasons of record and reasons set forth below.

Vignali teaches use of the FlowMetrix assay kit to measure cytokinelevels in an animal model. Cytokine levels were measured in sera and bronchoalveolar lavage. One of ordinary skill in the art would understand that the biological sample must be collected from the mammalian subject. Therefore, one of ordinary skill in the art would be motivated to include an instrument or sampling device to obtain said biological sample (ie, syringe, pipette, catheter) to increase efficiency of utilization of assay to determine cytokine levels.

Applicants traverse the rejection (Remarks of 20 March 2009, page 18, 2nd paragraph). The reasons for the traversal are:

Vignali does not disclose a kit, nor particularly, the kit as claimed. Thus, because there is no motivation initially to create or provide a kit, there is no motivation to add to such a kit a means for collecting biological samples. Even if one of skill in the art understood that a biological sample would need to be obtained, such information would not have led one of skill in the art to the present invention. Vignali does not suggest combining systems for measuring cytokines, and instructions for use of the systems and calculation of cytokine ratios into a kit or provide motivation or expectation of success for creating a kit. Thus, there is no expectation of success found in Vignali for creating a kit containing a means for collecting biological samples.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

The teachings of Vignali are discussed in detail above, and in previous office actions. Applicants' claim is vague and indefinite (see discussion above) and no particular kit is described. Thus, one of ordinary skill in the art would conclude that the FlowMetrix system used by Vignali, obtained from Luminex would fit the definition of a kit for measurement of cytokines.

With respect to instructions for use of the systems: case law teaches where the only difference between a prior art product (Multiplex system) and a claimed product (kit) is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. In re Ngai, 367 F.3d 1336, 1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004).

With respect to calculation of cytokine ratios: Once the cytokine levels are determined using the FlowMetrix system, one of ordinary skill in the art would certainly know how to calculate ratios and be able to interpret ratios of cytokines obtained from samples before and after treatment.

As summarized above, one of ordinary skill in the art would recognize that some instrument or device must be utilized to obtain a biological sample from a mammalian subject. In the interest of efficiency, one would be motivated to include such an instrument with a kit for measuring cytokine levels.

The rejection of Claims 1, 3, 5, 16, 17, 19, and 20 under 35 U.S.C. 103(a) as being unpatentable over Togawa et al. (2002 Am J. Physiol, Gastrointestinal Liver Physiol 283:G187-G195) is maintained for reasons of record and for reasons set forth below.

To summarize: Togawa et al. teach administration of lactoferrin (treatment method) to TNBS-induced colitis model in rats (abstract and page G187, 2nd column, last paragraph, G188, 1st column, 3rd paragraph). The reference teaches measurement of anti- and pro-inflammatory cytokines in samples of inflamed colon seven days after

TNBS administration (page G188, 2nd column, 2nd paragraph, last paragraph bridging G189, 1st column, 1st paragraph, page G191, 1st column, last paragraph bridging 2nd column, first paragraph and Figure 5) and in samples of colons from untreated animals with TNBS-induced colitis (equivalent of tissue biopsies). The reference teaches measurement of the pro-inflammatory cytokines TNF-α, and IL-1β, and the anti-inflammatory cytokines IL-4, and IL-10 by ELISA assays (abstract and G189, 1st column, 1st paragraph) and comparing cytokine levels in treated rats to those in untreated rats (Figure 5). Togawa et al does not teach measuring the level of anti-inflammatory and pro-inflammatory cytokines before administering treatment, or determining the ratio of levels of anti-inflammatory cytokine to level of pro-inflammatory cytokine.

However, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Togawa et al, which measures cytokine levels in control, untreated animals with TNBS-induced colitis and in experimental, treated animals with TNBS-induced colitis and measure cytokine levels in a biological sample (tissue biopsy) before administration of treatment (equivalent to untreated animals) and after treatment (equivalent of treated animals). A person of ordinary skill in the art would have been motivated to make those modifications because Togawa et al teach "although it is not possible to extrapolate findings from animal models to the clinical situation, these data suggest that lactoferrin is potentially attractive as a therapeutic strategy for the treatment of inflammatory bowel disease" (page G194, 1st column, 1st paragraph), thus suggesting clinical experimentation to determine efficacy of the described therapeutic approach. The skilled artisan, following the teaching of Togawa et al, would be motivated to measure cytokine levels before treatment in a clinical setting, instead of measuring levels in control animals, because the skilled artisan would be aware that this protocol is routine in clinical studies. Furthermore, knowing the results of measurements of cytokine levels (as shown, for example, in Figure 5), one would be motivated to compute ratios as a way of determining shifts in patterns of cytokine levels. One would reasonably expect success

because method of measuring cytokine levels in biological samples is well known in the art, and is taught by Togawa et al.

Applicants traverse the rejection (Remarks of 20 March 2009, page 19, last paragraph, bridging page 20, 3rd paragraph). The reasons for the traversal are:

Towaga details only one particular experiment in rats using induced colitis. Towaga does not provide any suggestion or motivation to study 'before and after' results, or to set up such experiments, without controls. Towaga does not suggest studying ratios of cytokines to establish and analyze shifts in patterns of cytokine levels to evaluate efficacy of treatment. In particular, Towaga does not suggest or provide motivation for the particular cytokines and ratios as claimed. Towaga simply induces colitis in rats and compares cytokine levels to those of normal, control rats in conjunction with studying physical aspects of the induced disease in order to determine whether lactoferrin is effective against the induced colits.

The Applicants maintain that there is no suggestion, motivation or predictability to do *completely different* clinical experiments, with completely different protocols and subjects, or to use or analyze 'before and after' data in a clinical setting simply because such things could be able to be done. There is simply no suggestion in Towaga that would lead one skilled in the art of animal studies to make the jump to a very different human study.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

The Togawa et al reference teaches the following fact pattern:

1. An experimental rat model of IBD is established by treating rats with TNBS, thus inducing colitis, an inflammatory bowel disease.

2. One group of animals with TNBS-induced colitis rats is treated with a test treatment compound (lactoferrin) and a second group of animals with TNBS-induced colitis, the control group, is treated only with saline.

Thus contrary to Applicants assertions, Togawa compares cytokine levels in treated animals with TNBS-induced colitis to cytokine levels in untreated animals with TNBS-induced colitis, not normal controls. One of ordinary skill in the art would consider the control, untreated group in an animal model of TNBS-induced colitis to be the equivalent of a mammalian subject before treatment, as recited in the claims and the lactoferrin treated group in an animal model of TNBS-induced colitis to be the equivalent of a mammalian subject after treatment.

3. Pro-inflammatory and anti-infammatory cytokines are measured in samples of inflamed colons (biopsy samples) from animals treated with lactoferrin (treatment) or saline (control). The reference teaches measurement of the pro-inflammatory cytokines TNF-α, and IL-1β, and the anti-inflammatory cytokines IL-4, and IL-10 by ELISA assays and comparing cytokine levels in treated rats to cytokine levels in untreated rats. Thus, Togawa et al. teaches changes in levels of pro- and anti-inflammatory cytokines as a result of treatment of IBS; the reference teaches correlation of changes in cytokine levels with other changes in IBD tissue. These changes may be indicative of efficacy of treatment for IBS. One of ordinary skill in the art would consider this measurement of efficacy of treatment to be the equivalent of measuring changes in cytokine levels in mammalian subject before and after treatment.

While Togawa et al do not teach measuring the level of anti-inflammatory and pro-inflammatory cytokines before administering treatment, or determining the ratio of levels of anti-inflammatory cytokine to level of pro-inflammatory cytokine before and after treatment, it would have been obvious to the person of ordinary skill in the art at the time the invention was made, treating IBS patients, to measure cytokine levels in a biological sample before administration of treatment and after treatment to assess efficacy of treatment. One of ordinary skill would be motivated to do so because the art recognizes and Togawa et al teach "there is a disturbed balance between proinflammatory and anti-inflammatory cytokines in inflammatory bowel disease" (page G187, 2nd column, 1st paragraph). A person of ordinary skill in the art would have been motivated to make those modifications in clinical protocol because Togawa et al teaches "TNBS-induced colitis is a well-established model that is similar to human

inflammatory bowel disease" (page G192, 2nd column, 2nd paragraph) and suggest clinical experimentation to determine efficacy of the administration of lactoferrin for treatment of IBS. The skilled artisan, following the teaching of Togawa et al, would be motivated to measure cytokine levels before treatment in a clinical setting, instead of measuring levels in untreated animals in an experimental animal model, as the artisan would be aware of that such study design is a standard protocol in clinical research, and would realize that it would be less expensive, more efficient and more ethical to test cytokine levels in patients before and after treatment instead of having an untreated group of patients (equivalent to untreated animals with TNBS-induced colitis) as taught by Togawa et al. and comparing said group to treated patients. Furthermore, knowing the results of measurements of cytokine levels (as shown, for example, in Figure 5), one would be motivated to compute ratios of anti-inflammatory to pro-inflammatory cytokines as an easy way of determining shifts in patterns of cytokine levels. One would reasonably expect success because methods of measuring cytokine levels in biological samples is well known in the art, and is taught by Togawa et al.

The rejection of Claims 18 and 21 under 35 U.S.C. 103(a) as being unpatentable over Togawa et al. as applied to claims 1, 17 and 20 in view of Vignali et al. (cited above and in previous Office Action) is maintained for reasons of record and for reasons set forth below.

Applicants traverse the rejection (Remarks of 20 March 2009, page 21, 2nd paragraph, bridging page 22, 1st paragraph). The reasons for the traversal are:

While one could analyze the cytokine levels of Towaga with such a system as disclosed in Vignali, one would not have arrived at the claimed method of determining the efficacy of a treatment of inflammatory diseases of the bowel in mammals *in vivo.* Towaga and Vignali together do not suggest or provide motivation or expectation of success for a clinical method, using samples from a biological subject, in which particular cytokine levels are determined and ratios analyzed, as claimed. In addition, because Claims 18 and 21 depend ultimately from Claim 1 which the Applicants assert

is novel and non-obvious over the cited documents, the Applicants submit that Claims 18 and 21 are also novel and non-obvious over the cited documents.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

In response to applicants' arguments that the Togowa reference does not render the methods of the instant application: As stated above, Togawa et al suggest clinical experimentation to determine efficacy of the administration of lactoferrin. The clinical researcher would be motivated to measure cytokine levels before treatment in a clinical setting, instead of measuring levels in untreated animals with TNBS-induced colitis as taught by Togawa et al, since such is standard practice in clinical research.

Togawa et al teach measuring levels of at least one anti-inflammatory cytokine and at least one pro-inflammatory cytokine in a biological sample by ELISA using assay kits with the quantitative immunometric sandwich enzyme immunoassay technique. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Togawa et al and substitute the multiplex assay taught by Vignali for the ELISA assay taught by Togawa et al. One would be motivated to make this substitution, and anticipate success since both assays involve immunological methods of measuring cytokine concentrations and Vignali teaches a more efficient method of quantifying the concentration of 15 cytokines simultaneously. As stated above, knowing the results of measurements of cytokine levels, one would be motivated to compute ratios as a way of determining shifts in patterns of cytokine levels.

The rejection of Claims 6-8 under 35 U.S.C. 103(a) as being unpatentable over Togawa et al. as applied to claim 1 in view of Blumberg et al. (1999. Current Opinion in Immunology 11:648-656) is maintained for reasons of record and for reasons set forth below.

The teachings of Togawa et al are outlined in detail above and in previous office actions. Togawa et al. teaches measurement of anti-inflammatory cytokines IL-4 and

IL-10 and measurement of pro-inflammatory cytokines TNF-α, IL-1β and IL-6 in untreated animals with TNBS-induced colitis and treated animals with TNBS-induced colitis. Knowing the results of measurements of cytokine levels (as shown, for example, in Figure 5), one would be motivated to compute ratios of anti-inflammatory to pro-inflammatory cytokines as an easy way of determining shifts in patterns of cytokine levels.

Togawa et al do not teach method wherein the ratio of anti-inflammatory cytokine to pro-inflammatory cytokine is the ratio of the level of IL-10/to the level of IL-12 (claim 6), or the level of TGF-β/to the level of IL-12 (claim 7), or the level of IL-10/ to the level of IFN-γ (claim 8). As previously noted, Blumberg et al. teach immune responses uniquely involved in IBD pathogenesis and note the importance of balance of pro-inflammatory cytokines such as **IFN-γ, TNF**, and **IL-12** and anti-inflammatory cytokines such as **IL-10** and **TGF-β** (abstract). The reference teaches that IL-12 is a key factor in the pathogenesis of the TNBS-induced colitis model (the model taught by Togawa et al) and induces overproduction of IFN-γ and TNF (page 650, 2nd column, last paragraph bridging page 651, 1st column, 3rd paragraph). Blumberg et al also teach that mucosal inflammation can be viewed as a failure of production of suppressor cytokines such as TGF-β and IL-10 (page 652, 2nd column, 2nd paragraph).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Togawa et al and substitute measurement of the pro-inflammatory cytokines taught by Blumberg et al (IFN-γ and IL-12) for the pro-inflammatory cytokine taught by Togawa et al (TNF-α, IL-1β and IL-6) and the anti-inflammatory cytokine taught by Blumberg et al (TGF-β) for the anti-inflammatory cytokine taught by Togawa et al (IL-10). Once measurement of these cytokines is accomplished, the calculation of ratios would be obvious as a way of monitoring changes in the balance of levels of pro- to anti- inflammatory cytokines. One would be motivated to make these modifications because both references teach disturbed balance between proinflammatory and anti-inflammatory cytokines in inflammatory bowel disease and Blumberg et al teach IFN-γ, TNF, and IL-12 are pro-

inflammatory cytokines involved in pathology of IBD and IL-10 and TGF-β are anti-inflammatory cytokines whose expression may be down-regulated in IBD. Thus, the pro-inflammatory cytokines IFN-γ, TNF, and IL-12 and the anti-inflammatory cytokines IL-10 and TGF-β are considered to be art-recognized equivalents in the pathology of IBD.

Applicants traverse the rejection (Remarks of 20 March 2009, page 22, last paragraph, bridging page 23, 3rd paragraph). The reasons for the traversal are:

Towaga does not suggest establishing or analyzing any ratios of cytokines, nor particularly the claimed ratios. Blumberg also does not suggest establishing or analyzing ratios of cytokines, nor the importance or utility thereof for testing or determining efficacy of a potential treatment.

Even if one were to have combined the disclosure of Towaga and Blumberg, one would not have arrived at the Applicants' invention, as claimed. Simply because levels of various cytokines can be measured and various experiments can be run in animal models does not provide the requisite motivation or expectation of success for selecting and measuring particular cytokines and monitoring ratios thereof, in humans, for screening and evaluating the efficacy of a potential treatment. Neither Towaga nor Blumberg provide motivation for methods of screening compositions for efficacy in treating diseases of the bowel in humans.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

In response to traversal of teachings of Togawa et al, see discussion above. Blumberg et al teach the importance of a balance of pro-inflammatory cytokines such as IFN-γ, TNF, and IL-12 and anti-inflammatory cytokines such as IL-10 and TGF-β in the pathology of IBD. Both Togawa et al. and Blumberg et al. teach the importance of disturbed balance between proinflammatory and anti-inflammatory cytokines in inflammatory bowel disease. Thus, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of

Togawa et al and substitute measurement of the pro-inflammatory cytokines taught by Blumberg et al (IFN-γ and IL-12) for the pro-inflammatory cytokine taught by Togawa et al (TNF-α, IL-1β and IL-6) and the anti-inflammatory cytokine taught by Blumberg et al (TGF-β) for the anti-inflammatory cytokine taught by Togawa et al (IL-10), since the references teach all of these cytokines are important in the etiology and progression of IBD. One would be motivated to measure changes in cytokine levels, since Togawa et al teach changes in cytokine levels in response to therapeutic administration of lactoferrin. Knowing the results of measurements of cytokine levels (as shown, for example, in Figure 5), one would be motivated to compute ratios of anti-inflammatory to pro-inflammatory cytokines as an easy way of determining shifts in patterns of cytokine levels.

The rejection of Claims 11 and 12 under 35 U.S.C. 103(a) as being unpatentable over Togawa et al. as applied to claim 1 in view of Bing et al (1998. World J Gastroenterology 4:252-255) is maintained for reasons of record and for reasons set forth below.

To summarize, the teachings of Togawa et al. are outlined in detail above and in previous office actions. Togawa et al does not teach a method of determining the efficacy of a treatment of inflammatory disease of the bowel in mammals wherein said biological sample comprises peripheral blood mononuclear cells (PBMC) with *in vitro* stimulation, wherein said in vitro stimulation comprises stimulation with a mitogen.

Bing et al. teach assaying production of inflammatory cytokines such as TNF-α and IL-6 by PBMCs isolated from patients with IBS stimulated by a mitogen, PHA (phytohemagglutinin).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Togawa et al and substitute measurement of the pro-inflammatory cytokines and anti-inflammatory cytokines in mitogen-stimulated PBMCs, the system taught by Bing et al, for measurement of cytokines in colonic tissue from untreated and lacto-ferrin treated animals with TNBS-

induces colitis (equivalent of “before" and “after” measurements of cytokine levels in mammalian subjects). One of ordinary skill in the art would have been motivated to make these modifications because the skilled artisan would recognize that it would be simpler and less invasive to obtain PBMCs from blood samples drawn from patients than to obtain biopsies from colon tissue. Once measurement of these cytokines is accomplished, the calculation of ratios would be obvious as a way of monitoring changes in the balance of levels of pro- to anti- inflammatory cytokines.

Applicants traverse the rejection (Remarks of 20 March 2009, page 24, 2nd paragraph, bridging page 25, 1st paragraph). The reasons for the traversal are:

Towaga does not suggest establishing or analyzing any ratios of cytokines, nor particularly the claimed ratios, and that one of skill in the art would not have been led by Towaga's rat study to perform a completely different human study. Bing studied stimulated release of various cytokines by PBMCs in patients with UC. However, Bing does not suggest or provide motivation, expectation of success or predictability for the particular claimed methods of measuring particular cytokines, measuring cytokine levels in the same subject before and after treatment, and using particular ratios of cytokines in methods of evaluating efficacy of potential treatments. The cited documents do not suggest using particular cytokines to screen potential treatments for inflammatory diseases of the bowel, nor provide motivation or expectation of success for developing a screening method for evaluating potential treatments for inflammatory diseases of the bowel.

Applicant’s arguments have been fully considered but are not found to be persuasive for the following reasons:

In response to traversal of teachings of Togawa et al, see discussion above. Contrary to Applicants’ assertion, Togawa et al measure levels of a pro- and anti-inflammatory cytokine recited in the methods of the claimed invention, IL-10 and IL-4. It would be obvious to one of ordinary skill in the art to modify the teachings of Togawa et al, which teaches comparing cytokine levels in biopsies of tissue from untreated animals with TNBS-induced colitis to cytokine levels in biopsies of tissue from treated animals

with TNBS-induced colitis and measure cytokine levels before treatment and after treatment in a clinical setting for reasons set forth above and measure such cytokines in stimulated PBMCs before and after treatment of IBD. The Bing reference teaches measurements in supernatants of stimulated PBMCs as an alternative method for evaluating changes in cytokine levels in mammalian subjects (biopsy vs. stimulated PBMCs). Computing ratios of levels of anti-inflammatory cytokine to pro-inflammatory cytokine is a mental exercise or calculation step and would not confer patentability on the method of the instant invention. Once measurement of the recited cytokines is accomplished, the calculation of ratios would be obvious to the skilled artisan as a way of monitoring changes in the balance of levels of pro- to anti- inflammatory cytokines.

Conclusions:

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHULAMITH H. SHAFER whose telephone number is (571)272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao, Ph.D. can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. H. S./
Examiner, Art Unit 1647

/Manjunath N. Rao /
Supervisory Patent Examiner, Art Unit 1647